REMARKS

Claims 1 to 8 as amended are present for purposes of prosecution.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.

Claim 1 has been amended to include standard therapy of 2-3 INR full dose warfarin as disclosed at page 1, lines 12 to 15 and page 2, lines 10 to 12 of the Specification.

In addition, Claim 1 has been amended to include low dose therapy of warfarin as less than 2.0 INR as disclosed in the Specification at page 2, line 15.

The Examiner contends that:

> "Independent claim 1 recites the term 'standard therapy'. The specification does not clearly define the term and leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear. Although the specification discloses that therapy for idiopathic venous thromboembolism (VTE) typically includes 'a 5 to 10 day course of intravenous or subcutaneous heparin followed by a 3 to 12 month period of oral anticoagulation with full dose warfarin, adjusting the dosage to an international normalized ratio (INR) between 2.0 and 3.0'. It is not clear the term 'standard therapy' refers to 'a 5 to 10 day course of intravenous or subcutaneous heparin followed by a 3 to 12 month period of oral anticoagulation with full dose warfarin, adjusting the dosage to an international normalized ratio (INR) between 2.0 and 3.0' or other known therapy. It is considered that the meaning of the claims should be clear from the wording of the claim alone."

Claim 1 has been amended to include the definition of full-dose warfarin used in standard therapy as "2.0 to 3.0 INR".

In view of the foregoing, it is believed that Claims 1 to 8 are in compliance with 35 U.S.C. §112, second paragraph.

A discussion of Applicants' invention as claimed follows.

Therapy for idiopathic venous thromboembolism (VTE) with warfarin typically includes a 3 to 12 month period of oral anticoagulation with full dose warfarin, adjusting the dosage to an International Normalized Ratio (INR) between 2.0 and 3.0 (references 1-4 set out on page 15 of the Specification). After cessation of anticoagulation, however, recurrent VTE is a major clinical problem with rates estimated between 6 and 9 percent annually (references 5,6, page 15 of the Specification). While extended use of full-dose warfarin is associated with reduced rates of

recurrent deep vein thrombosis and pulmonary embolism (references 2-4), community based studies have consistently found this approach to be associated with substantial risk of major hemorrhage. For example, in observational studies, use of full-dose warfarin is associated with major bleeding rates between 5 and 9 percent (references 7-9, page 15 of the Specification). Similarly, an annual major hemorrhage rate of 3.8 percent was observed in a recent full-dose warfarin trial despite careful on-site anticoagulation monitoring (reference 3).

By contrast, low-intensity warfarin has been shown in several settings to have a low risk of bleeding when used on a chronic basis and may require less frequent monitoring. Further, experimental data indicate that low-intensity warfarin is effective in reducing biochemical markers of coagulation such as factor VII activity and levels of prothrombin fragment F_{1+2} (references 10,11, pages 15 and 16 of the Specification). No clinical data, however, are available evaluating low-intensity warfarin for long-term venous thrombosis prophylaxis. Thus, the cited Ridker reference describes a protocol for the PREVENT clinical study and not the results. The results obtained from the PREVENT study are set out in the Examples on pages 3 to 14 of the Specification.

In accordance with the present invention, it has been found that use of low-intensity warfarin over a long term significantly reduces incidence of recurrent venous thromboembolism (VTE).

Claim 1 as amended defines a method for inhibiting, preventing or reducing incidence of recurrent venous thromboembolism (VTE) in a patient who has previously undergone standard therapy for VTE (involving 3 to 12 months of full-dose warfarin using a targeted International Normalized Ratio [INR] between 2.0 and 3.0) and includes the step of administering to a patient who has previously undergone standard therapy for VTE a low dose of warfarin which is lower than the standard dose of warfarin administered in standard treatment of VTE. Thus, the low dose of warfarin will be less than 2 INR.

Claims 1 to 6 are rejected under 35 U.S.C. §102(b) as being anticipated by Ridker (Vascular Medicine, 1998, 3:67-73).

The Examiner contends that:

> "Ridker teaches the use of long-term (3-4 year regimen), low dose warfarin (INR 1.5-2.0) in patient with deep venous thrombosis and pulmonary embolism who undergone a 3-6 month period of full dose warfarin for preventing or reducing incidence of recurrent venous thromboembolism (abstract; page 71, column 1, lines 6-10 and 18-26), wherein the range of low-dose warfarin is as small as 1-2mg daily (page 70, column 1, line 14-19)."

It is submitted that Applicants' invention as claimed is patentable over the cited Ridker reference.

As indicated above, Ridker discloses a protocol for the PREVENT study (prevention of recurrent venous thromboembolism) and describes the design used in the study. There is no disclosure or suggestion in Ridker of whether use of long-term low-dose warfarin will be effective in the secondary prevention of venous thromboembolism (VTE).

Applicants' invention as claimed is defined as a method for inhibiting, preventing or reducing incidence of recurrent venous thromboembolism. The Ridker reference only sets out a test design and does not disclose, suggest or give the slightest indication of 1) a method for, in fact, inhibiting, preventing or reducing incidence of VTE, or 2) that the study described would actually result in successfully inhibiting, preventing or reducing incidence of VTE. This is Applicants' inventive as claimed which is neither disclosed nor suggested by Ridker.

Clearly, it would not be obvious from the Ridker protocol that low dose warfarin would be effective in inhibiting, preventing or reducing incidence of recurrent venous thromboembolism. Why would one carry out the 3-4 year PREVENT study (involving a large number of patients and costing huge sums of money) if it would be obvious before the study that low dose warfarin would be efficacious in inhibiting, preventing or reducing incidence of recurrent venous thromboembolism? Warfarin, at the time of the start of the PREVENT study, was a known anticoagulant as disclosed by Millenson et al. (discussed above). However, what was not known or obvious was that low dose warfarin would be effective in inhibiting, preventing or reducing incidence of recurrent VTE.

Nowhere in Ridker or any other reference is there a suggestion or clue that low dose warfarin would be so effective.

In view of the foregoing, it is clear that Ridker does not anticipate or make obvious Applicants' invention as claimed. Accordingly, it is submitted that Claims 1 to 6 are patentable over Ridker.

Claims 7 to 8 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ridker (Vascular Medicine, 1998, 3:67-73), and further in view of Millenson et al. (Blood, 1992, 79(8):2034-2038).

The Examiner contends that:

> "The teaching of Ridker has been discussed in above 35 U.S.C. §102(b) rejection.

Milenson is being supplied as a supplemental reference to demonstrate the routine knowledge in the art in determining 'low dose of warfarin' to achiever the target INR range of 1.3 to 1.6. The reference teaches the use of mean daily dose 3.7 mg of warfarin in normal patient or mean 5.5mg of warfarin in patient who is on medications known to decrease the bioavailability of warfarin in achieving the targeted INR range of 1.3 to 1.6 (page 2035, column 2, lines 28-43).

The teaching of Ridker differs from the claimed invention in the specific dosage of warfarin, 'within the range from about 3 to about 6 mg daily' and 'about 4 mg daily'.

However, those of ordinary skill in the art would have been readily determine effective dosages as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information herein. Appropriate dosages may be ascertained through use of established assays for determining dosages in conjunction with appropriate dose-response data. The final dosage regimen will be determined by the attending physician, considering the drug's specific activity, the responsiveness of the subject, the age, condition, body weight, diet, the severity of any infection, time of administration and other clinical factors. As evidenced by Milenson, those or ordinary skill in the art would be able to determine appropriate low dosage levels of warfarin which lies within the range of the claimed dosage range, 'from about 3 to about 6mg daily' or 'about 4mg daily' in achieving the targeted INR range of 1.5-2.0."

It is submitted that Applicants' method as claimed in Claims 7 and 8 (as well as Claims 1 to 6) is patentable over a combination of Ridker and Millenson et al.

The Ridker reference has been discussed above and the comments there set out apply here as well.

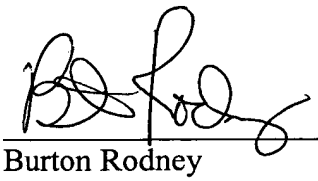
Millenson et al. disclose that treatment with warfarin using 1.7 to 2.5 INR is efficacious for many indications. However Millenson et al. does not disclose or suggest that low dose warfarin could be employed to inhibit, prevent or reduce incidence of recurrent venous thromboembolism. Thus, a combination of Ridker taken with Millenson et al. is no more relevant to Applicants' method as claimed as is Ridker taken alone. The combination of Ridker and Millenson et al. does not

disclose or suggest a method for inhibiting, preventing or reducing incidence of recurrent venous thromboembolism using low dose warfarin.

Accordingly, it is submitted that Applicants' invention as claimed in Claims 7 and 8 (as well as Claims 1 to 6) is patentable over a combination of Ridker and Millenson et al.

In view of the foregoing, it is submitted that Claims 1 to 8 as amended in compliance with 35 U.S.C. §112 and are patentable over the cited Ridker alone or Ridker taken with Millenson et al. Accordingly, a prompt allowance of Claims 1 to 8 is believed to be in order and such action is respectfully requested.

Respectfully submitted,



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Date: October 26, 2006